High density lipoprotein cholesterol and triglycerides as markers of angiographically assessed coronary artery disease

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Abstract
Serum triglycerides, high density lipoprotein (HDL) cholesterol, and total cholesterol were measured in 698 patients examined by angiography. The ratio of HDL cholesterol to total cholesterol was significantly lower in patients with single, double, and triple vessel disease than in patients without disease. The serum concentration of triglyceride was significantly higher in patients with single, double, and triple vessel disease than in those without coronary artery disease. Similar proportion of patients with coronary artery disease and without had serum cholesterol concentrations of ≥6·5 mmol/l, but total cholesterol was significantly higher in patients with single, double, and triple vessel disease than in those without. HDL cholesterol (<1·0 mmol/l), triglycerides (>2·0 mmol/l), and the ratio of HDL cholesterol to total cholesterol (<0·20) were significantly better than total cholesterol as indicators of coronary risk.

Since 1959, when Albrink and Man suggested that raised concentrations of serum triglyceride might be related to the pathogenesis of ischaemic heart disease,[1] several investigators have measured lipids in healthy individuals and those with this disease.[2-4] Clinical studies have established that a raised serum concentration of total cholesterol is an aetiological factor in coronary artery disease.[5 6] Fewer data are available on the possible value of raised concentrations of triglyceride in predicting the occurrence of the disease in apparently healthy men. In a follow up prospective study in Sweden the occurrence of new events of ischaemic heart disease was related to serum triglycerides and cholesterol, which were risk factors for coronary artery disease that were independent of each other. The highest risk of coronary artery disease was associated with a combined increase of those two serum lipids.[7] Follow up studies from other areas in Sweden confirmed that serum triglycerides were a risk factor for ischaemic heart disease.[8 9] There are more recent both primary and secondary prevention studies, in which a beneficial effect was closely related to a reduction of serum triglycerides rather than to the reduction in serum cholesterol.[10 11] The serum concentration of total cholesterol in Finland is exceptionally high (mean 6·3 mmol/l) even in healthy people and the relative importance of

lipid components is not necessarily similar to that in other countries.

The aim of this study was to determine whether total cholesterol, high density lipid (HDL) cholesterol, and triglycerides are discriminators of coronary artery disease. In addition, we attempted to find out whether lipid concentrations are related to the extent of disease.

Patients and methods
We studied 698 patients aged 29–69 years admitted during 1985–7 to Tampere University Hospital for elective coronary angiography for the investigation of chest pain. Lesions in coronary arteries were graded visually from 0 to 4: 0 = normal, 1 = >50% stenosis in one vessel, 2 = >50% stenosis in two vessels, 3 = >50% stenosis in three vessels. Coronary angiography was performed by the Judkins technique via the right femoral artery. Twenty four hours before catheterisation serum total cholesterol, HDL cholesterol, and triglycerides were measured after a 12 hour fast. All patients were ambulant up until the day on which serum lipids were measured, at least three months after myocardial infarction. We used a cut off value of 6·5 mmol/l for total cholesterol and a cut off value of 2·00 mmol/l for triglycerides, which were the arbitrary upper limits of normal at Tampere University Hospital. For HDL cholesterol we used a cut off value of 1·0 mmol/l, which was the lower limit of normal. For the ratio of HDL cholesterol to total cholesterol we used a cut off value of 0·20, which is useful index of the risk of coronary artery disease.[12]

The patients were divided into four groups on the basis of the angiographic results: 63 patients did not have clinically important coronary artery disease (that is stenosis of <50% of the transluminal diameter in all segments), 124 patients had single vessel disease, 192 patients double vessel disease, and 319 patients triple vessel disease. Table 1 shows the smoking habits, the use of β blockers, previous myocardial infarction, and the sex ratio in the four groups.

Serum cholesterol was measured by the Monotest kit from Boehringer Mannheim with an Olli C semiautomated analyser (Kone Oy, Finland). The polyethyleneglygol precipitation method was used to measure HDL cholesterol together with the Monotest for cholesterol. Concentrations of serum triglycerides were measured by an enzymatic method (Boehringer Mannheim).

Table 1   Percentage of smokers, use of β blockers, previous myocardial infarction, and male sex in relation to findings of coronary angiography

	No lesion (n = 63)	Single vessel (n = 124)	Double vessel (n = 192)	Triple vessel (n = 319)	All
Smokers	10**	22	29	16	20
Use of β blockers	63*	75	81	84	80
Previous myocardial infarction	22***	63	61	60	56
Male sex	62*	81	88	88	84

*p < 0·05, **p < 0·01, ***p < 0·001 compared with other groups.

The data from the four groups of patients were compared by an analysis of variance and when the F ratio was significant we used a Student-Newman-Keuls test. Triglyceride values were log transformed before statistical analysis but untransformed values are given in the text and tables. To analyse the frequency of patients by a χ^2 test we combined the three groups with coronary artery disease to give a group with disease and one without. A Bartlett-Box test and a multiple discriminant analysis were used to assess the lipid values as discriminators of coronary artery disease.

Results

Table 2 summarises the data on serum lipids for each group of patients, defined according to the number of coronary arteries with ≥50% stenosis. The mean values for total cholesterol were significantly (p < 0·01) higher in patients with single, double, and triple vessel disease than in those without disease. Serum HDL cholesterol was significantly (p < 0·001) higher in patients without coronary artery disease than in patients with single, double, or triple vessel disease. The ratio of HDL to total cholesterol was significantly (p < 0·001) lower in patients with single, double, and triple vessel disease than in patients without disease. The mean values for triglycerides were significantly (p < 0·01) higher in all patients with disease than in patients without.

Total cholesterol was ≥6·5 mmol/l in 20 (31·8%) patients without disease and in 273 (43·0%) patients with disease; the difference was not statistically significant (table 3). HDL cholesterol was ≤1·0 mmol/l in 28·6% of 63 patients without disease and in 52·1% of 635 patients with disease (p < 0·001). The best discriminators between patients without and with disease was serum triglyceride (>2·0 mmol/l) and in the ratio of HDL to total cholesterol (<0·20) (p < 0·001) (table 3). There was a significant inverse correlation

between HDL cholesterol and serum triglycerides (r = −0·382, p < 0·001). Multiple discriminant analysis showed that the ratio of HDL to total cholesterol was a better indicator of coronary artery disease than other lipid values.

Discussion

The Study Group of the European Atherosclerosis Society recommends dietary and other measures to reduce risk in most people with serum cholesterol values of 5·2–6·5 mmol/l.[13] Lipid lowering drugs should then be considered if total cholesterol remains at 6·5 mmol/l or higher. In the present study, however, 31·8% patients without disease and 43·0% with disease had total cholesterol concentrations of ≥6·5 mmol/l. This non-significant difference between patients with and without disease was equal whatever the different cut off points of total cholesterol (for 0·1 mmol/l intervals between 6·0 and 7·0 mmol). These results show that total cholesterol measurement alone is not a good discriminator.

There are no firm recommendations on triglyceride measurement in risk assessment and treatment for raised triglycerides. Nevertheless, reanalysis of the Framingham data[14] indicated that serum triglycerides are independently predictive of coronary artery disease in patients with low serum concentrations of HDL cholesterol. Serum triglyceride concentrations are probably important in secondary prevention after myocardial infarction, because serum concentrations are higher in such patients[11] than in healthy individuals. In the Helsinki Heart Study gemfibrozil considerably reduced triglycerides (by 35%) but only modestly reduced low density lipoprotein (LDL) cholesterol (8% decrease) and increased HDL cholesterol (10% increase).[10] The effects on serum concentrations of triglycerides, low density lipoprotein cholesterol, and high density lipoprotein cholesterol contributed to a beneficial outcome.

Those treated with cholestyramine in the seven year Lipid Research Clinics study showed mean reductions in plasma concentrations of total and low density lipoprotein cholesterol of 13 and 20% respectively; an average increase of 3% in HDL cholesterol and the slight rise in triglycerides were not significant.[15] A 17% reduction in all definite end points for ischaemic heart disease was seen in the Lipid Research Clinics study and a 34% reduction in the Helsinki Heart study, in which the greatest relative change in serum lipid

Table 2   Age, serum total cholesterol, HDL cholesterol, triglycerides, and the ratio of HDL cholesterol to total cholesterol in patients without coronary artery disease and in those with single, double, or triple vessel disease

Variable	No lesion (n = 63)		Single vessel (n = 124)		Double vessel (n = 192)		Triple vessel (n = 319)		Statistical significance in ANOVA
Age	52·2	(0·91)	49·4	(0·74)	53·5	(0·67)	54·9	(0·33)	
Total cholesterol (mmol/l)	5·93	(0·15)	6·34	(0·12)	6·53	(0·09)	6·52	(0·06)	p < 0·01
HDL cholesterol (mmol/l)	1·29	(0·05)	1·13	(0·03)	1·10	(0·03)	1·07	(0·01)	p < 0·001
Triglycerides (mmol/l)	1·77	(0·11)	2·39	(0·13)	2·50	(0·13)	2·59	(0·11)	p < 0·01
HDL:Total cholesterol	0·22	(0·01)	0·18	(0·01)	0·17	(0·01)	0·17	(0·01)	p < 0·001

Values are given as mean (SEM). ANOVA, analysis of variance. In Student-Newman-Keuls test the statistical difference was significant between the group without coronary artery disease and all other groups with coronary artery disease, but not between groups with single, double, and triple vessel disease.

Table 3 Percentage of patients in relation to serum lipid

	No lesion (n = 63) (%)	Disease (n = 635) (%)	χ^2	Significance
Total cholesterol > 6·5 mmol/l	31·8	43·0	3·2	NS
HDL cholesterol < 1·0 mmol/l	28·6	52·1	15·3	p < 0·001
Triglycerides > 2·0 mmol/l	28·6	52·4	21·4	p < 0·001
HDL:Total cholesterol < 0·20	47·6	75·1	30·2	p < 0·001

concentrations was seen in serum triglycerides; this had only a small effect on the incidence of coronary artery disease.[16] Several American studies have shown that high concentrations of serum cholesterol are a significant coronary risk factor,[5 6] but in the United States the role of triglycerides remains controversial.

The importance of HDL cholesterol concentration was shown in several large epidemiological studies.[17 18] These surveys either indicated that individuals with low concentrations of HDL cholesterol have a higher prevalence of coronary artery disease or that a low HDL cholesterol concentration is a common antecedent of clinical coronary artery disease. There is evidence that triglycerides constitute an independently predictive risk factor for ischaemic heart disease in individuals with low serum concentrations of HDL cholesterol.[14] Raised triglycerides are a risk factor for ischaemic heart disease especially in middle aged men.[19] A reduced fibrinolytic capacity was often found in patients with myocardial infarction and hypertriglyceridaemia.[20] Moreover, follow up studies showed that hypertriglyceridaemia was an independent risk factor for reinfarction, an association possibly connected with a predisposition to thrombosis through a coexisting high concentration of plasminogen inhibitor.[21] Hypertriglyceridaemia is a thrombogenic factor rather than an atherogenic factor.

The findings of this study re-emphasise the importance of hypertriglyceridaemia and reduced HDL cholesterol as risk factors of coronary artery disease. Similar observations were reported in England, where a raised concentration of serum triglycerides was the best discriminator between patients and controls.[22] In this study there was an inverse correlation between HDL cholesterol and triglycerides. This may seem to be a central issue in the pathogenesis of atherosclerosis, since both high concentrations of triglyceride-rich lipoproteins (very low density lipoprotein) and low concentrations of HDL are well recognised lipid risk factors for arterial disease. It is possible that the primary disturbance responsible for the low HDL may ultimately lie in triglyceride metabolism and HDL could be a mediator between the basic metabolic defect and the vascular lesion.[23]

Follow up studies from Sweden confirm that raised concentrations of serum triglycerides are a risk factor for coronary artery disease.[7–9] In the present study serum triglyceride was a good discriminator, better than total cholesterol, between patients with coronary artery disease and those without. Triglyceride concentrations were significantly (p < 0·01) higher in those with single, double, and triple vessel disease

than in those without disease. A raised triglyceride concentration was a significant discriminator especially in one vessel disease, when patients tended to be young or middle aged, and their total cholesterol did not differ significantly from patients without disease. Patients without disease were significantly less likely to be smokers, to be taking β blockers, and to be men than in the other groups (table 2). Smoking and selective β_1 blockers do not influence serum total cholesterol, but can slightly increase triglycerides and reduce HDL cholesterol. The smaller proportion of men among those with normal findings on coronary angiography could contribute to the higher values of HDL cholesterol. Myocardial infarction and sudden unstable angina pectoris without earlier chest pain were more commonly found in those with one vessel disease than in those with double or triple vessel disease. Also HDL cholesterol alone was a better discriminator than total cholesterol. The best discriminator in this study was a low ratio of HDL cholesterol to total cholesterol.

Total cholesterol does not discriminate between healthy people and patients with coronary artery disease. Before patients with hypercholesterolaemia (> 6·5 mmol/l) are treated HDL cholesterol should be measured. The results of the present study suggest that the ratio of HDL cholesterol to total cholesterol was a better indicator of coronary risk than HDL cholesterol alone, total cholesterol, or triglycerides. Serum triglycerides give a wider discrimination than serum total cholesterol in identifying not only patients with multivessel disease but also those with important single vessel disease.

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